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Response to "Comment on 'A simple molecular thermodynamic theory of hydrophobic hydration'" [J. Chem. Phys. 119, 10448 (2003)]

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The infinite dilution excess chemical potential of a hard spherical cavitylike solute in water is, in general, a function of the temperature *T*, density of water ρ_w, and cavity radius *R*,

$$\mu_s^{*\infty}=kTf(T,\rho_w,R). \tag{1}$$

Following standard thermodynamic relationships, the excess partial molar hydration entropy can be written as

$$\overline{s_s^{*}}^{\infty}=-kf+kT\left(\alpha_w\rho_w\frac{\partial f}{\partial\rho_w}\bigg|_T-\frac{\partial f}{\partial T}\bigg|_{\rho_w}\right), \tag{2}$$

where α_w is the thermal expansion coefficient of pure water. In order to derive the criterion for entropy convergence from this expression, the functionality of *f* must be known. Considerations from an information theory (IT) approach to cavity hydration indicate that to an excellent approximation *f* is independent of temperature and can be factored as

$$f(T,\rho_w,R)=\gamma(\rho_w)\,\eta(R). \tag{3}$$

In this case the partial molar excess entropy is given by

$$\overline{s_s^{*}}^{\infty}=k\eta\left(-\gamma+T\alpha_w\rho_w\frac{\partial\gamma}{\partial\rho_w}\right). \tag{4}$$

Convergence of the entropies of cavities of all sizes then occurs when $\overline{s_s^{*}}^{\infty}$ is zero. This is satisfied when

$$\alpha_w=\frac{\gamma}{T\rho_w}\left(\frac{\partial\gamma}{\partial\rho_w}\right)^{-1}. \tag{5}$$

It finds $\gamma(\rho_w)=\rho_w^2$.[1] The resulting condition for entropy convergence is $\alpha_w=(2T)^{-1}$.

In our recently developed statistical thermodynamic mean-field model for an aqueous mixture with nonpolar van der Waals (vdW) solutes, a similar factorization of the "volume" contribution to the hydration entropy, which dominates the entropy, follows from the vdW excluded volume contribution to the chemical potential.[2] In this model $\gamma(\rho_w)=\rho_w/(1-\rho_w b_w)$, where b_w is the vdW excluded volume of water. It follows that entropy convergence is obtained when

$$\alpha_w=\frac{1-\rho_w b_w}{T}. \tag{6}$$

This condition is remarkably similar to that obtained from IT in that entropy convergence depends only on properties of water alone and occurs when α_w is a fraction of the inverse temperature.

Figure 1 compares the entropy convergence criterion, Eq. (6), to α_w obtained from our mean-field model [Eq. (C14) in Ref. 2]. The thermal expansion coefficient of water is negative at low temperature, and vanishes at the temperature of maximum density of water at 4 °C. Above this temperature, α_w is positive and increases with increasing temperature. At 329 K the two curves intersect, α_w satisfies Eq. (6) and entropy convergence is observed (see Fig. 8 in Ref. 2). While the expression for α_w is complicated, depending on both vdW and hydrogen-bonding interactions, in the limit of no hydrogen-bonding α_w is given by the vdW expression,

$$\alpha_{\mathrm{vdW}}=\frac{1-\rho_w b_w}{T-2a_{ww}\rho_w(1-\rho_w b_w)^2}, \tag{7}$$

where a_{ww} is the vdW attractive parameter for water–water interactions. For realistic, i.e., positive, values of a_{ww}, this expression is always greater than the derived convergence criterion (Fig. 1). Expressing the thermal expansion coefficient of water as $\alpha_w=\alpha_{\mathrm{vdW}}+\alpha_{\text{H-bond}}$,[3] the hydrogen-bonding term then is such that it reduces the thermal expansion coefficient, i.e., $\alpha_{\text{H-bond}}<0$. At the temperature of maximum density, the hydrogen-bonding and vdW contributions exactly balance, while the hydrogen-bonding interaction is reduced with increasing temperature, and $\alpha_w\rightarrow\alpha_{\mathrm{vdW}}$. α_w satisfies Eq. (6) at a unique temperature and entropy convergence is observed. So we conclude that aqueous hydrogen-bonding is necessary for entropy convergence to occur in our model and that the bare vdW fluid does not display such behavior.

In his comment, Graziano subdivides the solute partial molar excess entropy into two separate contributions:[4] Cavity growth and the reorganization of water as a result of the cavity perturbation. Graziano ascribes water's thermal expansion coefficient largely to hydrogen-bond fluctuations

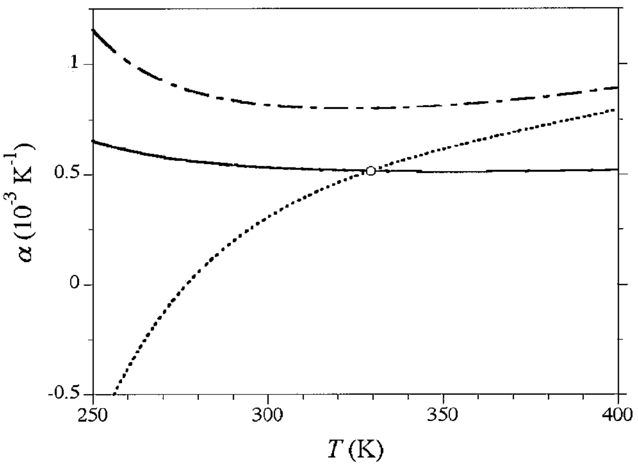

FIG. 1. Comparison of the thermal expansion coefficients of water, a van der Waals fluid, and entropy convergence condition along the one bar isobar for liquid water. The short-dashed line corresponds to α_w from Eq. (C14) in Ref. 2. The dotted–dashed line corresponds to $\alpha_{\rm vdW}$ from Eq. (7). The solid line corresponds to the entropy convergence criterion given by Eq. (6). $\alpha_{\text{H-bond}}$ is the difference between α_w and $\alpha_{\rm vdW}$. The point indicates the temperature (329 K) at which α_w satisfies Eq. (6) and entropy convergence is observed in liquid water. We note that the entropy convergence criterion shown are predictions from our mean-field model (Ref. 2), while experimentally entropy convergence is observed at temperatures near 385 K (Ref. 1).

(“transient H-bond reorganization”). As a result, he concludes that the solvent reorganization entropy, which is proportional to α_w, is a result of hydrogen-bond reorganization surrounding the hard-sphere cavity. While this picture is plausible, it is not strictly borne out by the model when we consider the relative importance of the vdW and hydrogen-bonding contributions to thermal expansion. Figure 1 shows that below the temperature of maximum density $\alpha_{\rm vdW} < -\alpha_{\text{H-bond}}$, hydrogen-bonding dominates, and water contracts upon heating. Above this temperature, however, $\alpha_{\rm vdW} > -\alpha_{\text{H-bond}}$, the vdW contribution dominates, and water expands with further heating. At the entropy convergence temperature, well above the temperature of maximum density, we find that $\alpha_{\rm vdW}$ and $\alpha_{\text{H-bond}}$ are equal to 8×10^{-3} and -3×10^{-3} K^{-1}, respectively. Thus entropy convergence is determined by the interplay between vdW and hydrogen-bonding contributions to α_w, and the conclusion that hydrogen-bonding dominates the solvent reorganization entropy is erroneous.

Our observation that α_w depends sensitively on both hydrogen-bonding and vdW contributions to the equation-of-state makes the conclusion that the anomalously high excess heat capacity of hydrophobic hydration is a result of hydrogen-bond reorganization suspect as well. We do note, however, that the temperature derivative of α_w, which plays a role in the heat capacity [Eq. (5) of Ref. 3], is strongly dependent on hydrogen-bond contributions since $\alpha_{\rm vdW}$ is less sensitive to temperature than α_w (Fig. 1). We also note that the microscopic interpretation of thermodynamic quantities such as the thermal expansion coefficient, calculated from our phenomenological model for hydrogen-bonding in the presence of a hydrophobic solute[2] is not straightforward. While these interpretations may appear intuitively reasonable, a direct connection is not possible because water structure around the solute is not incorporated into the model's partition function.[2]

In conclusion, we agree with Graziano that the entropy for hydration of a hydrophobic cavity can be decomposed into cavity growth and solvent reorganization contributions. However, to attribute solvent reorganization and the excess heat capacity solely to hydrogen-bond restructuring is overly simplistic even within the context of our model. Hydrogen-bonding certainly plays a crucial role in the peculiar thermodynamics of hydrophobic hydration, as manifested in the unique equation-of-state properties of water.[1,2] Molecular-level interpretations from our mean-field model should be used with caution, and more fundamental, microscopically-based models should be invoked to verify their accuracy.

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[1] S. Garde, G. Hummer, A. E. Garcia, M. E. Paulaitis, and L. R. Pratt, Phys. Rev. Lett. **77**, 4966 (1996).

[2] H. S. Ashbaugh, T. M. Truskett, and P. G. Debenedetti, J. Chem. Phys. **116**, 2907 (2002).

[3] The equation for α_w [Eq. (C14) in Ref. 2] involves nonlinear combinations of vdW and hydrogen-bonding contributions and cannot be expressed analytically as a sum of vdW and hydrogen-bonding contributions. Nevertheless, we can define $\alpha_{\text{H-bond}}$ operationally as $\alpha_w - \alpha_{\rm vdW}$.

[4] G. Graziano, J. Chem. Phys. **119**, 10448 (2003).